

In the Specification

Please add following paragraph as the first paragraph on page 1 of the specification, following the title and before TECHNICAL FIELD.

Page 1, paragraph 1 (New)

This application is a divisional of U.S. Patent Application Serial No. 10/161,289, now U.S. Patent No. _____, issued _____, which was a divisional of U.S. Patent Application Serial No. 09/787,623, now U.S. Patent No. 6,420,415, issued July 16, 2002 which was the National Phase filing of International Patent Application No. PCT/JP99/05103, filed September 20, 1999.

Please replace the third paragraph starting on page 20 of the specification with the following paragraph.

Page 20, Paragraph 3 (Currently Amended)

Such “5- or 6-membered aromatic heterocyclic group” may for example be furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, **pirazolyl** **pyrazolyl**, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, etc.

Please replace the sixth paragraph starting on page 24 of the specification with the following paragraph.

Page 24, Paragraph 6 (Currently Amended)

Such “aromatic heterocyclic group” may for example be 5- or 6-membered aromatic monocyclic heterocyclic group (for example furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, etc.), etc. and ~~a~~ an 8- to 12-membered aromatic condensed heterocyclic group such as an aromatic condensed heterocyclic group (for example, benzofuranyl, isobenzofuranyl, benzothienyl, indolyl, isoindolyl, 1H-indazolyl, benzindazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, benzopyranyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, ~~sinolynyl~~ cinnolinyl, quinazolyl, quinoxanyl, phthalazinyl, naphthylidiny, purinyl, pteridinyl, carbazolyl, ~~α -carborynyl, β -carborynyl, γ -carborynyl, α -carbolinyl, β -carbolinyl, γ -carbolinyl~~, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, ~~phenoxathiynyl~~ phenoxathiinyl, thianthrenyl, phenanthridinyl, ~~phenanthronyl~~ phenanthrenyl, indolydiny, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl, etc.) (preferably, a heterocyclic ring formed by condensing a 5- or 6-membered aromatic monocyclic heterocyclic group described above with a benzene ring, or a heterocyclic ring formed by condensing the same or different 2 heterocyclic rings of 5- or 6-membered aromatic monocyclic heterocyclic groups described above).

Please replace the third paragraph on page 88 of the specification with the following paragraph.

Page 88, Paragraph 3 (Currently Amended)

NMR (Nuclear Magnetic Resonance) spectra were measured using a *VARIAN* model Gemini-200 spectrometer (^1H -NMR:200MHz) or a *BRUKER* model DPX-300 spectrometer (^1H -NMR:300MHz). An internal standard was tetramethylsilane and all δ values are represented in ppm. Abbreviations employed here are described below.

CDCl_3 : deuterio chloroform, DMSO-d_6 : deuterio dimethylsulfoxide, Hz: ~~Herz~~ Hertz, J:

Coupling constant, m: Multiplet, q: Quartet, t: Triplet, d: Doublet, s: Singlet, br: Broad, dd:

Double doublet, dq: Double quartet.

Example 1 3-Mercapto-1-(4-phenoxybenzylpyrrolidine-2,5-dione

Please replace the third paragraph on page 149 of the specification with the following paragraph.

Page 149, Paragraph 3 (Currently Amended)

220 mg (0.74 mmol) of (R)-4-mercapto-1-(4- phenoxybenzyl)pyrrolidin-2-one obtained in Example 25 was dissolved in 2 ml of chloroform, treated with 59 mg (0.81 mmol) of methyl ~~isothocyanate~~ isothiocyanate and 5.1 μl (catalytic amount) of triethylamine, and stirred under nitrogen atmosphere for 12 hours. The reaction mixture was concentrated under reduced pressure and purified by preparative thin layer chromatography (eluent: n-hexane: ethyl acetate (1:2)) to obtain 75 mg (yield: 27%) of the title compound as a colorless oil.

^1H -NMR (300MHz, CDCl_3)

δ : 8.30-7.98 (1H, m), 7.35-6.92 (9H, m), 4.56-4.49 (1H, m), 4.44 (1H, d, J=14.8Hz), 4.36 (1H, d, J=14.7Hz), 3.89 (1H, dd, J=11.1, 6.9Hz), 3.37 (1H, dd, J=11.1, 3.0Hz), 3.19 (3H, d, J=7.8Hz), 3.02 (1H, dd, J=17.9, 8.9Hz), 2.55 (1H, dd, J=17.7, 4.0Hz)

Example 77 (3R)-5-Oxo-1-(4-phenoxybenzyl)pyrrolidinyl ethyldithiocarbonate

Please replace the second paragraph on page 150 of the specification with the following paragraph.

Page 150, Paragraph 2 (Currently Amended)

220 mg (0.74 mmol) of (R)-4-mercapto-1-(4- phenoxybenzyl)pyrrolidin-2-one obtained in Example 25 was dissolved in 2 ml of chloroform, treated with 71 μ l (0.81 mmol) of ethyl ~~isothiocyanate~~ isothiocyanate and a previously prepared solution of 5.1 μ l (catalytic amount) of triethylamine and 2.1 μ l (catalytic amount) of acetic acid in 0.1 ml of chloroform, and stirred under nitrogen atmosphere for 2 days. The reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with 0.1 N hydrochloric acid and then with saturated brine, and dried over anhydrous sodium sulfate. The reaction mixture was concentrated under reduced pressure and purified by preparative thin layer chromatography (eluent: n-hexane: ethyl acetate (1:2)) to obtain 211 mg (yield: 74%) of the title compound as a pale pinkish oil.

¹H-NMR (300MHz, CDCl₃)

δ : 7.61-6.91 (10H, m), 4.51-4.38 (3H, m), 3.91-3.84 (1H, m), 3.74-3.32 (3H, m), 3.06-2.97 (1H, m), 2.55-2.48 (1H, m), 1.26 (3H, t, J=7.2Hz)

Example 78 (4R)-4-[(Methoxycarbonyl)disulfanyl]-2-oxo-1-(4-phenoxybenzyl)pyrrolidine

Please replace the second paragraph on page 227 of the specification with the following paragraph.

Page 227, Paragraph 2 (Currently Amended)

200 mg (0.51 mmol) of cis-5-hydroxymethyl-4-methanesulfonyloxy-1-(4-phenoxybenzyl)pyrrolidin-2-one obtained in Example 20 was dissolved in 5 ml of chloroform, treated with 51 mg (0.61 mmol) of ~~dihydropyran~~ dihydropyran and 1 drop of conc. hydrochloric acid and stirred at room temperature for 3 hours.

Please replace the third paragraph on page 228 of the specification with the following paragraph.

Page 228, Paragraph 3 (Currently Amended)

300 mg (0.74 mmol) of the carboxylic acid product thus obtained was dissolved in 15 ml of N,N-dimethylformamide, and treated with 153 mg (0.80 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and 108 mg (0.80 mmol) of hydroxybenzotriazole and stirred at room temperature for 15 minutes. To this reaction mixture, a solution of 112 mg (0.80 mmol) of glycine ethyl ester hydrochloride and 81 mg (0.80 mmol) of triethylamine dissolved in 3 ml of (0.35 mmol) dimethylformamide was added dropwise at room temperature, and the mixture was stirred for 3 hours. The reaction mixture was extracted with ethyl acetate and diluted hydrochloric acid, and the ethyl acetate layer was washed with water and concentrated, and the residue was subjected to column chromatography on silica gel eluting with chloroform: methanol (98:2) to obtain 160 mg (yield: 44%) of a 5- ~~ethoxycarbonylmethylaminocarbonyl~~ ethoxycarbonylmethylaminocarbonyl product as a colorless oil.

Please substitute the following paragraph for the second paragraph on page 229 of the specification.

Page 229, Paragraph 2 (Currently Amended)

170 mg (0.35 mmol) of the 5- ~~ethoxycarbonylmethylaminocarbonyl~~
ethoxycarbonylmethylaminocarbonyl product thus obtained and 198 mg (1.73 mmol) of potassium thioacetate were subjected to a method similar to that in Example 183 to obtain 41 mg (yield: 25%) of trans-4-acetylthio-5-ethoxycarbonylmethylaminocarbonyl-1-(4-phenoxybenzyl)pyrrolidin-2-one as a colorless oil.

¹H-NMR (200MHz, CDCl₃)

d : 7.40-6.90 (10H, m), 5.17 (1H, d, J=15.1Hz), 4.26-3.80 (5H, m), 4.24 (2H, q, J=7.2Hz), 3.05 (1H, dd, J=8.1, 18.0Hz), 2.34 (1H, dd, J=1.5, 18.0Hz), 2.33 (3H, s), 1.30 (3H, t, J=7.2Hz)

Example 187 trans-5-Aminocarbonyl-4-acetylthio-1-(4-phenoxybenzyl)pyrrolidin-2-one

Please replace the fifth paragraph on page 249 of the specification with the following paragraph.

Page 249, Paragraph 5 (Currently Amended)

75 µl of a sample containing the recombinant human MMP-13, 200 mM sodium chloride, 20 mM calcium chloride, 0.1% Brij 35, 1mM 2-~~metcaptoethanol~~
mercaptoethanol, 200 mM tris-HCl buffer solution (pH7.5) and a test substance at various ~~concentration~~ concentrations was treated with 25 µl of 40µM MOCAc-Pro-Leu-Gly-Leu-A₂pr(DNP)-Ala-Arg-NH₂ (PEPTIDE KENKYUSHO) to initiate a reaction and kept at 37°C for 2 hours, and then 100 µl of 500 mM sodium acetate-HCl buffer solution (pH3.0) was added to terminate the reaction.